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RETENTION INDICES OF DIMETHYLFORMAMIDINES, DIMETHYL-ACETAMIDINES AND TETRAMETHYLGUANIDINES ON A NON-POLAR COLUMN*

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SUMMARY

The retention indices of series of dimethylformamidines, dimethylacetamidines, tetramethylguanidines and corresponding primary amines and also substituted hydrocarbons on a GE SE-30 column were determined. Limitations of the additivity rule in the prediction of retention indices are discussed and the correlation method is proposed instead. It was found that the prediction of retention indices of compounds containing an amidino group, based on the retention indices of the corresponding substituted hydrocarbons, may lead to erroneous results. Much better results are obtained if the retention indices of the corresponding primary amines are used for this purpose.

INTRODUCTION

Amidines are biologically active compounds[1,2] and are particularly promising as antibacterial and antiprotozoal drugs[3]. It has been found that the introduction of an amidine group into a molecule of an antibiotic, such as penicillin, may enhance its antibacterial activity[4-6]. For these reasons, methods of synthesis and the activity of amidines are of interest. A study on amino group exchange in amidines carried out in our laboratory[7,8] required reliable method for the simultaneous determination of very similar amidines and related compounds in reaction mixtures. The most suitable means for this purpose are chromatographic methods, but unfortunately they have not been extensively applied to amidines[9], although a method for the characterization of amidines as their picrates by thin-layer chromatography has been described[10].

More recently, it has been shown that gas chromatography can be successfully applied to both the qualitative as well as quantitative determination of amidines[11]. Moreover, the use of dimethylformamide dimethylacetal (DMF-DMA) as derivatization reagent for the primary amino group has been widely used[12-15]. As a result of derivatization, the N^1,N^1-dimethylformamidino group is formed and therefore the

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* Amidines, Part XIV; for Part XIII see ref. 19.

possibility of predicting the retention indices of compounds containing an amidino group and, as a consequence, identification of the starting amino compounds has become important.

For this reason, a systematic study of the relationship between the structures of amidines and their retention indices was undertaken. Moreover, because compounds that contain an amidine group are usually less volatile than the corresponding compounds that contain an amino group, it is interesting to know the limits of the applicability of gas chromatography for the determination of these compounds.

In this work the Kováts retention indices[16,17] of three series of compounds containing the amidine ($N = C–N$) group, each including at least 24 compounds, were determined on a non-polar GE SE-30 column.

The compounds investigated have the general formula

$$R_x\text{–}N = C\text{–}N \underset{\displaystyle CH_3}{\overset{\displaystyle \overset{\textstyle R_c}{|} \quad \nearrow CH_3}{\searrow}}$$
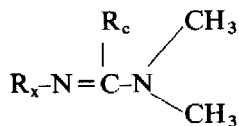
R_c = H N^1,N^1-dimethylformamidines (FDM)
R_c = CH_3 N^1,N^1-dimethylacetamidines (ADM)
R_c = $N(CH_3)_2$ N^1,N^1,N^3,N^3-tetramethylguanidines (TMG)

Using the same column, the retention indices of primary amines $R_x NH_2$ (PA) and substituted hydrocarbons $R_x H$ were determined for comparative purposes.

EXPERIMENTAL

Materials

Compounds containing an amidine group were synthesized and isolated accordingly to procedures described elsewhere: FDM[18], ADM[19], TMG[20]. The amines and hydrocarbon derivatives were of commercial grade. C_{12}–C_{20} n-alkanes were obtained from Applied Science Labs.

Gas chromatography

1A Chromatron Model GCHF 18.3.4 gas chromatograph with a flame-ionization detector, equipped with a 3 m × 3 mm I.D. column filled with 15% GE SE-30 silicone gum rubber on Chromosorb W AW (60–80 mesh), was used. The column temperature was maintained at 240°C for amidino compounds (FDM, ADM ,TMG) and at 180°C for amino compounds and the corresponding hydrocarbon derivatives. The carrier gas was nitrogen at a flow-rate of 25 ml/min. Samples of 1 μl of 0.1 M solutions in methanol (or n-pentane) were injected by means of a 10-μl Hamilton syringe.

Retention indices and dead-times were determined by regression analysis by the method of Grobler and Bálizs[21], as improved by Haken *et al.*[22] using the series of nine C_{12}–C_{20} n-alkanes, each time under the same conditions as for the studied sample.

RESULTS AND DISCUSSION

The retention indices obtained, with confidence intervals at a significance level of 0.05, calculated from at least five measurements, are given in Table I.

TABLE I

RETENTION INDICES OF DIMETHYLFORMAMIDINES (FDM), DIMETHYLACETAMIDINES (ADM), TETRAMETHYLGUANIDINES (TMG), CORRESPONDING PRIMARY AMINES (PA) AND SUBSTITUTED HYDROCARBONS (R_xH) ON A GE SE-30 NON-POLAR COLUMN

No.	R_x	R_xH*	PA*	FDM**	ADM**	TMG**
1	i-C_3H_7	300***	468 ± 6	806 ± 5	921 ± 10	992 ± 0
2	n-C_3H_7	300***	521 ± 2	864 ± 0	1001 ± 10	997 ± 4
3	i-C_4H_9		600 ± 0	938 ± 7	1057 ± 7	1163 ± 0
4	n-C_4H_9	400***	629 ± 2	985 ± 10	1098 ± 7	1160 ± 5
5	n-C_5H_{11}	500***	712 ± 3	1042 ± 3	1166 ± 6	1243 ± 4
6	n-C_6H_{13}	600***	848 ± 7	1166 ± 6	1284 ± 4	1352 ± 5
7	Cyclohexyl		857 ± 1	1229 ± 0	1322 ± 5	1398 ± 7
8	$C_6H_5CH_2$	788 ± 1	1035 ± 6	1408 ± 5	1441 ± 6	1615 ± 3
9	C_6H_5	681 ± 2	995 ± 0	1385 ± 7	1452 ± 7	1526 ± 3
10	3-F-C_6H_4	671 ± 3	1008 ± 3	1415 ± 8	1467 ± 4	1556 ± 4
11	4-F-C_6H_4	671 ± 3	1001 ± 4	1381 ± 6	1465 ± 3	1550 ± 4
12	3-CH_3-C_6H_4	788 ± 1	1088 ± 5	1491 ± 7	1547 ± 5	1596 ± 2
13	4-CH_3-C_6H_4	788 ± 1	1092 ± 5	1493 ± 6	1549 ± 6	1606 ± 7
14	3-OCH_3-C_6H_4	927 ± 1	1229 ± 6	1641 ± 4	1687 ± 2	1743 ± 2
15	4-OCH_3-C_6H_4	927 ± 1	1199 ± 5	1636 ± 4	1690 ± 2	1743 ± 2
16	3-Cl-C_6H_4	875 ± 2	1204 ± 1	1612 ± 3	1666 ± 2	1722 ± 3
17	4-Cl-C_6H_4	875 ± 2	1204 ± 3	1611 ± 4	1675 ± 6	1750 ± 3
18	3-OC_2H_5-C_6H_4	995 ± 2	1293 ± 1	1682 ± 3	1742 ± 2	1801 ± 5
19	4-OC_2H_5-C_6H_4	995 ± 2	1277 ± 1	1705 ± 3	1748 ± 3	1806 ± 1
20	3-Br-C_6H_4	964 ± 2	1295 ± 5	1709 ± 3	1766 ± 4	1835 ± 0
21	4-Br-C_6H_4	964 ± 2	1300 ± 3	1732 ± 1	1780 ± 4	1860 ± 6
22	4-I-C_6H_4	1075 ± 3	1411 ± 1	1850 ± 1	1896 ± 1	1982 ± 0
23	3-NO_2-C_6H_4	1103 ± 6	1446 ± 3	1877 ± 1	1928 ± 1	1996 ± 6
24	4-NO_2-C_6H_4	1103 ± 6	1560 ± 1	1968 ± 4	2009 ± 1	2146 ± 0
25	1-Naphthyl	1219 ± 2	1531 ± 1	1963 ± 2		
26	2-Naphthyl	1219 ± 2	1535 ± 2	1987 ± 3		

* Measured at 180°C.
** Measured at 240°C.
*** By definition.

There are several methods for the prediction of retention indices. Most of them consider the retention index as an additive function, and the simplest assume that the retention indices of compounds containing a certain functional group can be calculated by addition of a specific retention increment for this group to the retention indices of the corresponding hydrocarbons[23,24]. These methods, although not very precise, are commonly used on account on their simplicity.

The most accurate methods, such as that of Tacács and co-workers[25-32], are complicated and therefore impracticable for routine laboratory work; however, they have a certain theoretical value.

The prediction of retention indices for a particular series of compounds is usually based on those of corresponding compounds in another (standard) series. This is a typical problem of correlation analysis, in which the parameters (P_1) of compounds belonging to one series are expressed as a function, usually linear, of the parameters (P_2) of compounds with the same determined feature (x_i) in another series:

$$P_1(x_i) = AP_2(x_i) + B$$

It should be mentioned that the additivity scheme is a very particular case of a linear equation, where the slope of the correlation line (A) is by definition equal to 1.

We have correlated the retention indices of amidino compounds (FDM, ADM, TMG) with those of the corresponding hydrocarbons (R_xH) and primary amines (PA) in order to establish whether the slope of the correlation line (A) is really equal to 1 for both correlations, and which of them is better for use in an additivity scheme. The correlations are in the form

$$I_{amidine} = aI_{standard} + b$$

where I are retention indices.

The retention index depends to a small extent on temperature. Therefore, for the sake of higher accuracy of correlation, we attempted to have all retention indices in one series determined at one temperature. The most suitable temperature for the amidino compounds studied appeared to be 240°C, and for the standards used 180°C. Calculations were made by means of a least-squares method.

The regression coefficients (a and b) with confidence intervals calculated at a significance level of 0.05 and correlation coefficients (r) are given in Table II.

TABLE II

REGRESSION PARAMETERS OF RETENTION INDICES OF AMIDINES *VS.* RETENTION INDICES OF STANDARDS

Series	a	b	r	n
PA: R_xH	1.157 ± 0.068	169 ± 59	0.991	24
FDM: R_xH	1.278 ± 0.078	467 ± 68	0.991	24
PA	1.105 ± 0.024	280 ± 27	0.999	26
ADM: R_xH	1.202 ± 0.083	599 ± 68	0.989	22
PA	1.011 ± 0.025	450 ± 28	0.998	24
TMG: R_xH	1.242 ± 0.095	641 ± 78	0.987	22
PA	1.034 ± 0.035	500 ± 38	0.997	24

The results obtained indicate that the prediction of retention indices for compounds with the formula $R_xN = C(R)-N(CH_3)_2$ (FDM, ADM, TMG) from the retention indices of the corresponding substituted hydrocarbons R_xH cannot be based on the additivity rule, whereas a linear correlation scheme may be succesfully applied. It is also instantly seen that the slopes of the regression lines are different for different series of amidines.

It should be mentioned that the correlations obtained are of very good quality, as indicated by the correlation coefficients, but in each case studied the correlation with the retention indices of amines is much better than that with substituted hydrocarbons, and therefore has a higher predictive value.

For two correlations, *i.e.*, ADM and TMG *vs.* amines, the slope of the regression line, taking into account the accuracy limits, can be treated as equal to 1 and perhaps in this instance the additivity rule may be used. However, for FDM, the additivity rule cannot be applied with either R_xH or PA.

The much better correlation with amines, then with hydrocarbons is probably due to isomerism. The best examples are the benzyl and 3- and 4-tolyl derivatives (Table I, rows 8, 12 and 13). The retention indices of benzylamine and 3- and 4-toluidine are different, whereas taking for correlation the hydrocarbon R_xH for the three compounds in each series, the same retention index of 788 for toluene has to be used.

CONCLUSIONS

The results presented indicate that the additivity rule should be used very carefully for the prediction of retention indices because, depending on the standard compounds chosen and the range of retention indices considered, deviations from the additivity rule may cause errors. These errors can be particularly high when the predicted retention index is far from the range of retention indices taken for calculation of the increment on assumption of the additivity rule.

ACKNOWLEDGEMENTS

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